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THE EFFECTS OF CORONARY VASODILATATION ON CARDIAC PERFORMANCE D--ETC(U)

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TECHNICAL REPORT NO. 108

THE EFFECTS OF CORONARY VASODILATATION ON  
CARDIAC PERFORMANCE DURING ENDOTOXIN SHOCK

M. D. Peyton, L. B. Hinshaw, L. J. Greenfield, and R. C. Elkins

Prepared for Publication

in

Surgery, Gynecology and Obstetrics

University of Oklahoma Health Sciences Center  
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The heart has been sited as an end-organ of failure during the terminal stage of endotoxin shock and a myocardial depressant factor has been proposed as a precipitating agent (6). Experiments in our laboratory have demonstrated cardiac failure in the isolated canine heart confronted with endotoxin and lowered coronary arterial perfusion. In an attempt to determine the mechanism of failure, attention was directed toward evaluating the effects of decreased coronary perfusion and substrate delivery. Approximately 90% of hearts confronted with both endotoxin and lowered coronary perfusion failed as compared to 40% of those subjected to low coronary perfusion alone (5). Failure was not observed in hearts perfused with endotoxin but with normal ranges of coronary arterial pressures. Since lowered coronary perfusion was noted to be a significant factor in precipitating cardiac failure, attempts to increase perfusion and substrate delivery by dilating coronary vascular channels were evaluated. Sodium nitroprusside has been demonstrated to effectively dilate vessels by directly relaxing the smooth muscle of vessel walls and was therefore chosen to ascertain the effectiveness of coronary vasodilatation during periods of low perfusion pressure and endotoxin shock.

#### METHODS

The heart-lung complex was isolated in 11 small dogs (5-10 kg) and perfused with homologous blood from a large support dog (25-30 kg). Preload perfusion pressures were controlled by roller pump adjustments and coronary arterial perfusion pressures were determined by adjusting afterload by partial occlusion of the aortic outflow. Temperature was maintained at 37° C. The hematocrit was maintained at constant control levels by appropriate addition of dextran to the system. Coronary flow was measured directly from collection of coronary sinus effluent. The left ventricle and aorta were cannulated for



pressure measurements utilizing Statham pressure transducers and a direct-writing recorder. Recordings were also made of the support dog's systemic arterial pressure and heart rate, as well as the  $dp/dt$  and ECG of the isolated heart. Blood was analyzed for pH,  $PCO_2$ , and  $O_2$  content and calculations were made of  $O_2$  uptake (ml/min/100 gm L. V.), power (gm meters/sec.) and myocardial efficiency by methods previously reported (5). The preparation was studied at hourly intervals for four hours.

Following the recording of control values with the coronary arterial pressure stabilized at 100-110 mmHg, five control preparations (Group I) were administered an  $LD_{80}$  of E. coli endotoxin (Difco, Detroit), and aortic pressure was maintained at 40-50 mmHg. Six hearts (Group II) were perfused with sodium nitroprusside through the cannulated left atrium at a rate to stabilize coronary flow at one and one-half times control (30-60  $\mu$ g/min).

Statistical comparisons were made utilizing a student "t" test for paired groups.

### RESULTS

Mean left ventricular end-diastolic pressure (LVEDP) was significantly elevated in Group I from 4.4 mmHg to 10.3 mmHg following four hours and restoration of afterload pressures to control levels. (Figure 1) This was significantly greater ( $p < .05$ ) than the LVEDP value of 4.0 mmHg for Group II hearts receiving nitroprusside and restoration of afterload pressure.

Increasing afterload pressure at 25 mmHg increments at the end of four hours revealed significant elevation of LVEDP in hearts not receiving nitroprusside compared to physiologic values in those hearts perfused with the dilator ( $p < .05$ ). (Figure 2)

Coronary blood flow per 100 gm LV was significantly elevated in Group II from control values of 114 ml/min to 263 ml/min at the end of four hours and

at 100 mmHg afterload compared to 144 ml/min for Group I ( $p < .01$ ). Coronary blood flow was consistently increased above control ( $p < .05$ ) in Group II throughout the period of nitroprusside infusion. (Figure 3)

Oxygen delivery per 100 gm LV increased in Group II from 19 ml/min at control time to 40 ml/min at four hours and 100 mmHg afterload compared to insignificant increases in Group I hearts. (Figure 4) Oxygen extraction decreased from control values of 57% to 29.5% in Group II compared to stable values of approximately 60% for Group I ( $p < .01$ ). (Figure 5)

There were no significant differences between groups in regard to arterial blood gas values which remained within physiologic ranges. Heart rate did not change significantly for isolated hearts or for the support dog.  $DP/dt$  values did not differ significantly and there were no significant differences in myocardial efficiency between groups.

#### DISCUSSION

Coronary vasodilators have been utilized for the treatment of clinical angina pectoris while the mechanism of action of these agents has remained controversial. Schnaar (12) in 1971 demonstrated that trinitroglycerine and sodium nitrate relaxed large coronary arteries preferentially whereas adenosine as a non-nitrate compound relaxed small coronary arteries. Winbury (14) in 1969 also demonstrated the preference of nitrate compounds for dilating large coronary arteries for prolonged periods of time while having only a slight and transient effect on small coronary arteries. In addition, he noted that various non-nitrate coronary vasodilators such as dipyridamole, prenylamine, iproveratil, chromonor, lidoflazine, papaverine and aminophylline acted primarily to dilate small coronary arteries.

Moir (8), however, demonstrated a gradient in systolic coronary flow paralleling the intramyocardial tissue pressure in experimental animals,

stating the probability of coronary flow ceasing in the subendocardium during ventricular systole. In spite of this, coronary autoregulation causes vessels to dilate more in the subendocardium than in the subepicardium during diastole resulting in a greater diastolic flow in the former than in the latter. A nutritionally adequate coronary flow is therefore established for the endocardium during each cardiac cycle. Myocardial ischemia maximally dilates the subendocardial coronary vessels more readily than the epicardial vessels and thus removes the capacity for a greater reduction of diastolic coronary vascular resistance in the subendocardium. As a result, it is proposed that due to the inability to make up the systolic coronary flow deficit in the subendocardium, ischemia occurs earlier and more severely in the inner layers of the myocardium. Nitroglycerine in these studies has been postulated to increase flow to the subendocardium by reducing left ventricular wall tension. This is perhaps accomplished by venous capacitance as well as arterial dilatation lowering preload and afterload pressures. Since sodium nitroprusside acts by directly relaxing the smooth muscle of large and small vessel walls throughout the body, results similar to that of nitroglycerine should be expected.

In recent years, the canine heart has been the subject of intensive investigation regarding the effects of coronary blood flow and perfusion pressure on cardiac performance. Abel (1) utilized nitroglycerine in the isovolumetric isolated heart preparation and found that left ventricular contractility was augmented by increased coronary pressure and flow. Coronary flow seemed to be the major factor since an increase in flow without an increase in pressure produced similar augmentation.

Scharf (11) suggested that coronary capillary pressure is responsible for hemodirectional changes in cardiac contractility and coronary vascular volume. While utilizing the isolated canine heart and raising coronary



blood flow or coronary sinus pressure, he found a significant increase in cardiac performance with the increase in coronary sinus pressure providing a greater increase in function. Oxygen consumption was increased to a similar degree by both manipulations.

Templeton (13) also demonstrated a positive inotropic effect of increasing the coronary perfusion pressure from 60 to 95 mmHg or by infusing nitroglycerine in the isovolumetrically contracting canine heart.

Recent studies in our laboratories utilizing the cardiopulmonary bypass preparation in evaluating the effect of coronary perfusion pressure on myocardial performance during endotoxin shock revealed consistently better length-tension curves and pressure work in dogs in a state of systemic shock with high coronary perfusion than with low coronary perfusion (3). Results in this current study support the view that adequate coronary perfusion may be the most essential factor in preserving cardiac function during endotoxin shock.

The lowered LVEDP in hearts receiving nitroprusside reflected improved cardiac function compared to Group I hearts. Recent clinical reports by Guiha (4) of patients with intractable heart failure both from ischemic heart disease and cardiomyopathy treated with sodium nitroprusside revealed a significant reduction of LVEDP and a rise in cardiac output while mean arterial pressure was lowered and heart rate was slowed. Stroke volume and forward ejection were nearly doubled and echocardiographic studies indicated a reduction of left ventricular end-diastolic volume. Postulates to explain these results included that of a reduction of afterload by systemic vasodilatation with improved ejection fraction and a reduction of regurgitant flow through a dilated mitral valve. In the face of a heightened vascular resistance and outflow impedance, left ventricular wall tension, which is a function of chamber radius and pressure, remains high during ejection and stroke volume

is small. Therefore, by reducing afterload, the work of the left ventricle in generating wall tension is reduced, whereas forward stroke volume is increased. The increase in forward stroke volume was thought to minimize the reduction in arterial pressure that would otherwise have resulted in these patients from the vasodilator effect of the drug.

In our preparation, however, aortic afterload was held constant for both groups, but the significant increase in coronary vascular flow as demonstrated in those hearts receiving the dilator could effectively increase the percentage of ejection fraction perfusing the coronary vasculature. This direct coronary vasodilating effect could improve myocardial nutrition as demonstrated by the increased oxygen delivery and decreased oxygen extraction. The reduction in left ventricular diastolic pressure during infusion of the drug would favor subendocardial perfusion and augment cardiac performance. The failure of those hearts without nitroprusside infusion to increase oxygen extraction is also a significant finding which represents either impaired cellular metabolism or impaired delivery of oxygen to cells engaged in oxygen metabolism.

The contribution of the coronary vascular skeleton to ventricular wall tension might also be a significant factor with coronary vasodilatation reducing this component and its possible contribution to wall tension. Previous studies in our laboratory with endotoxin-shocked canine hearts with independently controlled coronary perfusion suggested that overperfusion of the coronary vasculature exacerbated failure with increased LVEDP and diastolic force (9). It was postulated that extravasation of fluid into the interstitial myocardial tissue occurred in the face of post-capillary constriction of coronary vessels. Other investigators have also suggested a propagation of myocardial edema leading to decreased cardiac compliance and increased LVEDP (7).

Salisbury's group (10) published some interesting findings of factors which initiate or influence edema formation in the canine heart. Perfusion of the canine heart with elevated coronary perfusion pressure elicited notable degrees of edema, which could also be enhanced by increased coronary venous pressures. Once the edema formation had been initiated by these or other factors, they observed that the heart continued to gain weight even when mean coronary pressure was lowered to normal values. They also noted a most interesting phenomenon in that myocardial edema did not cause the contractile strength of the heart to vary, but decreased its distensibility (i.e., increased diastolic pressure). The authors did not, however, rule out the possibility that myocardial edema might eventually oppose "shortening" of heart fibers, thereby reducing the ability of the ventricle to eject blood. Nevertheless, the major thrust of their work was brought to bear on the possible adverse effect of myocardial edema on diastolic filling with compromised cardiac output through reduction of stroke volume. The authors concluded that congestive heart failure is not necessarily associated with decreased ability of the heart to eject blood, but may be explained on the basis of decreased distensibility of the ventricle. Perhaps, therefore, coronary vasodilatation with nitroprusside could decrease fluid extravasation into the interstitium of the heart from damaged capillaries by reducing coronary vascular resistance and particularly coronary venous resistance.

Other proposals (2) of mechanisms of improvement of cardiac performance in failing hearts by infusion of nitroprusside concerns a lowered preload filling pressure occurring as a result of a decrease in venous return of blood to the right heart and pulmonary vasculature augmented by increased volume of peripheral capacitance vessels. This, however, was eliminated in our preparation by the constant preload perfusion and should not be a factor.



Although increased coronary flow was observed with decreased coronary vascular resistance, studies of regional flow in the myocardial tissue with additional consideration of possible arteriovenous shunting would be of interest, and further evaluation using radioactively tagged microspheres would perhaps be of value. Studies of an intact animal are of course mandatory in order to realize the inter-relation of the peripheral and central circulation and to extrapolate data to the clinical situation.

#### SUMMARY

Studies in our laboratories have suggested that endotoxin and lowered coronary arterial perfusion pressures are detrimental to cardiac performance and lead to failure. Prevention of cardiac failure in the isolated canine heart preparation confronted with endotoxin and decreased coronary perfusion pressure was possible by perfusing these hearts with sodium nitroprusside. Prevention of failure was manifested by a lowered LVEDP and was associated with increased coronary flow and decreased coronary resistance with increased oxygen delivery and decreased oxygen extraction. Possible explanations for improved performance by dilator perfusion include increased delivery of oxygen and nutrients to myocardial tissue as well as a reduction of ventricular wall tension by dilating the coronary vascular skeleton. Prevention of interstitial fluid extravasation into myocardial tissue by reducing over-perfusion of potentially damaged coronary vessels could serve to maintain myocardial integrity and ventricular compliance. The potential use of such therapy warrants further study with emphasis on evaluating the hemodynamics of the intact animal.

#### BIBLIOGRAPHY

1. Abel, R. M., and Reis, R. L. Effects of coronary blood flow and perfusion pressure on left ventricular contractility in dogs. *Circ. Res.*, 1970, 27:961.
2. Chatterjee, K., Swan, H. J. C. Vasodilator therapy in acute myocardial infarction. *Mod. Concepts Cardiovasc. Dis.*, 1974, 43:119.
3. Elkins, R. C., McCurdy, J. R., Brown, P. P., and Greenfield, L. J. Effects of coronary perfusion pressure on myocardial performance during endotoxin shock. *Surg. Gynecol. Obstet.*, 1973, 137:991.
4. Guiha, N. H., Cohn, J. N., Mikulic, E., Franciosa, J. A., and Limas, C. J. Treatment of refractory heart failure with infusion of nitroprusside. *N. Eng. J. Med.*, 1974, 291:587.
5. Hinshaw, L. B., Archer, L. T., Spitzer, J. J., Black, M. R., Peyton, M. D., and Greenfield, L. J. Effects of coronary hypotension and endotoxin on myocardial performance. *Am. J. Physiol.*, 1974, 227:1051.
6. Lefer, A. M. Role of a myocardial depressant factor in the pathogenesis of circulatory shock. *Fed. Proc.*, 1970, 29:1836.
7. McLaurin, L. P., Rolett, E. L., and Grossman, W. Impaired left ventricular relaxation during pacing-induced ischemia. *Am. J. Cardiol.*, 1973, 32:751.
8. Moir, T. W. Subendocardial distribution of coronary blood flow and the effect of antianginal drugs. *Circ. Res.*, 1972, 30:621.

BIBLIOGRAPHY (Con't)

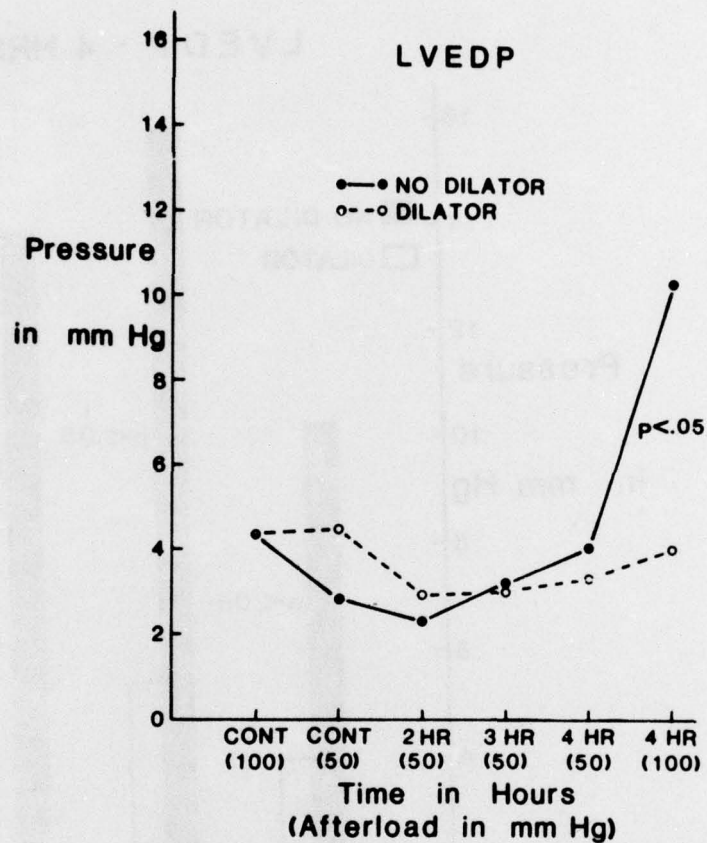
9. Peyton, M. D., Elkins, R. C., Hinshaw, L. B., Greenfield, L. J. Effects of coronary arterial perfusion on cardiac performance during endotoxin shock. *Fed. Proc.*, 1974, 33:297.
10. Salisbury, P. F., Cross, C. E., Katsuhara, K., and Rieben, P. A. Factors which initiate or influence edema in the isolated dog's heart. *Circ. Res.*, 1961, 9:601.
11. Scharf, S. M., and Bromberger-Barnea, B. Influence of coronary flow and pressure on cardiac function and coronary vascular volume. *Am. J. Physiol.*, 1973, 224:918.
12. Schaar, R. L., and Sparks, H. V. Response of large and small coronary arteries to nitroglycerin,  $\text{NaNO}_2$ , and adenosine. *Am. J. Physiol.*, 1972, 223:223.
13. Templeton, G. H., Wildenthal, K., and Mitchell, J. H. Influence of coronary blood flow on left ventricular contractility and stiffness. *Am. J. Physiol.*, 1972, 223:1216.
14. Winbury, M. M., Howe, B. B., and JrgHefner, M. A. Effect of nitrates and other coronary dilators on large and small coronary vessels: An hypothesis for the mechanism of action of nitrates. *J. Pharmacol. Exp. Ther.*, 1969, 168:70.



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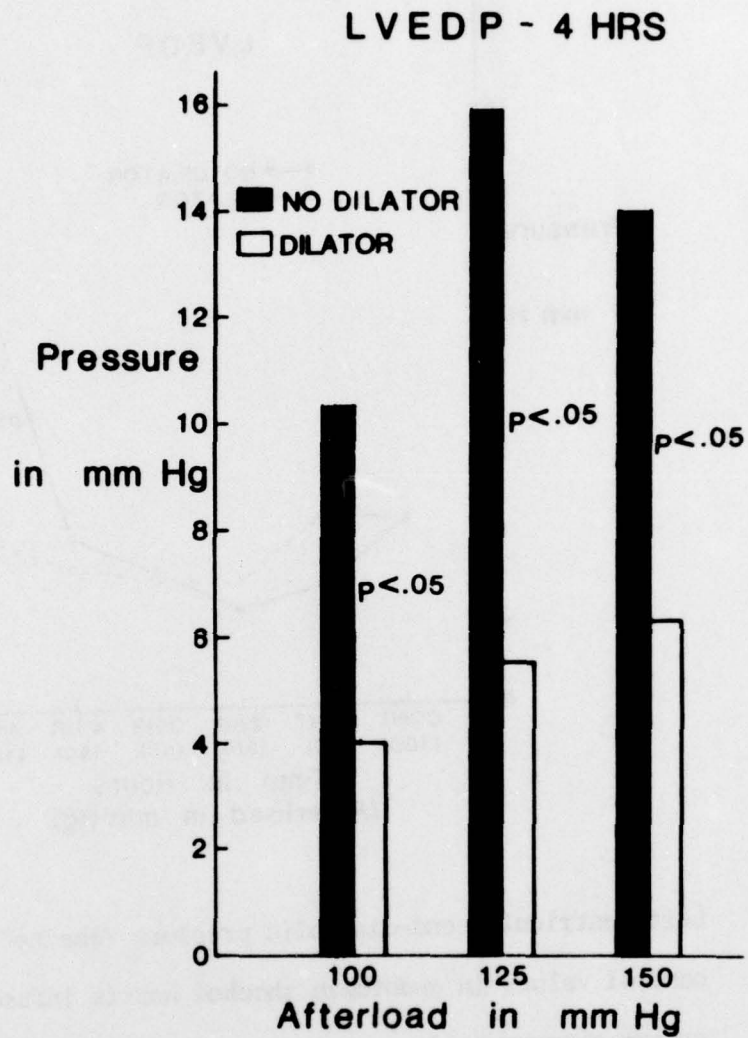
- Figure 1. Left ventricular end-diastolic pressure remained near control values in endotoxin shocked hearts infused with sodium nitroprusside compared to significant increases in hearts without dilator perfusion.
- Figure 2. Increased afterload stresses at the end of four hours yielded significant elevation of left ventricular end-diastolic pressure in control hearts compared to those perfused with sodium nitroprusside.
- Figure 3. Coronary blood flow was significantly increased in hearts perfused with sodium nitroprusside.
- Figure 4. Oxygen delivery was significantly increased in hearts receiving sodium nitroprusside compared to control hearts. Group I.
- Figure 5. Oxygen extraction was reduced significantly in hearts receiving sodium nitroprusside with no change observed in control hearts. Group I.

FIGURE 1



Left ventricular end-diastolic pressure remained near control values in endotoxin shocked hearts infused with sodium nitroprusside compared to significant increases in hearts without dilator perfusion.

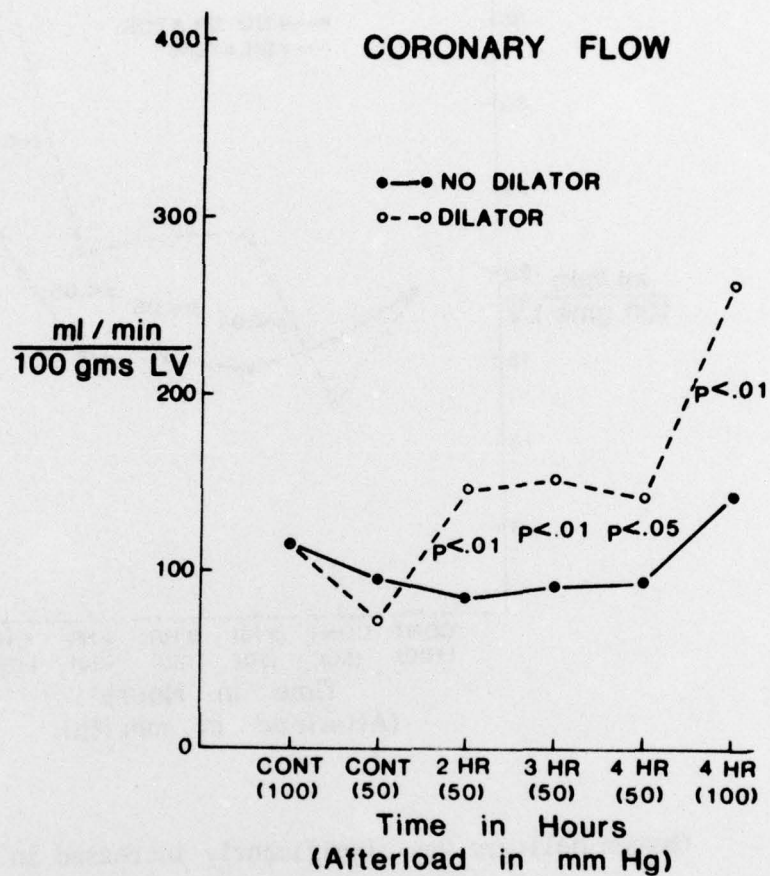
FIGURE 2



Increased afterload stresses at the end of four hours yielded significant elevation of left ventricular end-diastolic pressure in control hearts compared to those perfused with sodium nitroprusside.

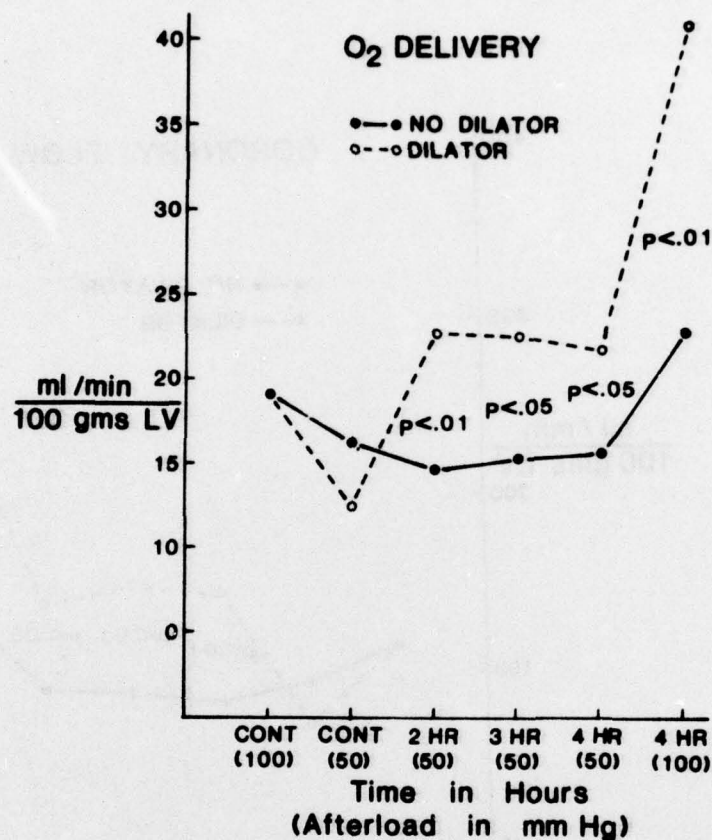


FIGURE 3



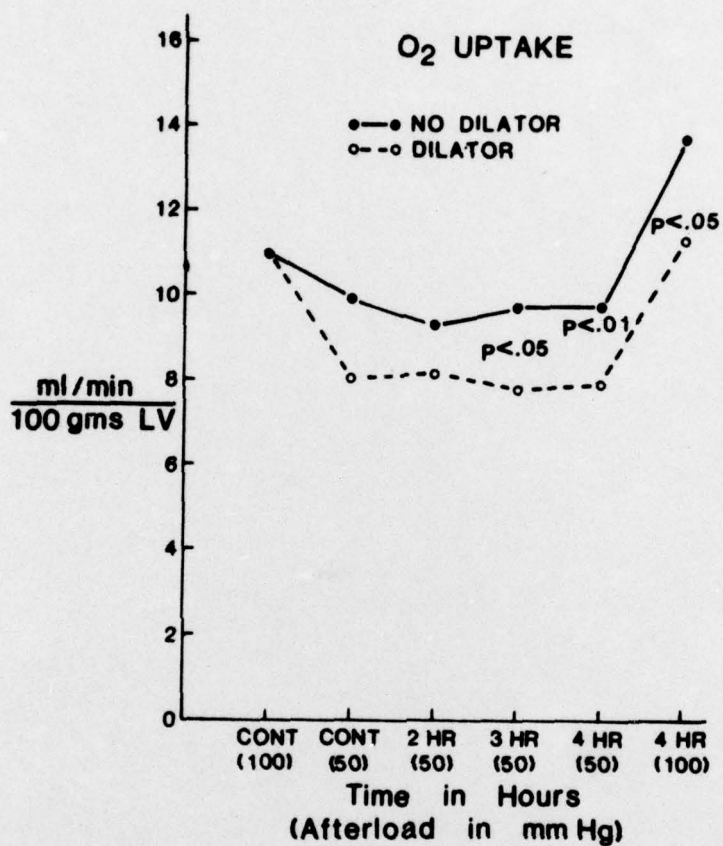
Coronary blood flow was significantly increased in hearts perfused with sodium nitroprusside.

FIGURE 4



Oxygen delivery was significantly increased in hearts receiving sodium nitroprusside compared to control hearts. Group I.

FIGURE 5



Oxygen extraction was reduced significantly in hearts receiving sodium nitroprusside with no change observed in control hearts. Group I.



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